

A CONTRIBUTION
TO THE
GENEALOGY

By ALEXA
Clinical T
Free

From the Laboratory

I.—Clinical a

A BOY, aged 14, was
the charge of Dr J
of epistaxis of three

History.—Patient
and frequently had
healthy. Nothing
parents Both pare

The expenses of c
J. J. J. J.

S.

A CONTRIBUTION TO THE HISTOLOGY AND GENEALOGY OF HÆMOPHILIA¹

By ALEXANDER GOODALL, M.D., F.R.C.P.,
Clinical Tutor, Royal Infirmary, Edinburgh ;
Freeland-Barbour Research Fellow

(From the Laboratory of the Royal College of Physicians, Edinburgh)

I.—Clinical and Histological Notes of a Case of Hæmophilia.

A BOY, aged 14, was admitted to the Royal Infirmary, under the charge of Dr James, on November 23rd, 1904, complaining of epistaxis of three weeks' duration.

History.—Patient's maternal grandmother was plethoric, and frequently had epistaxis. Maternal grandfather was healthy. Nothing is known regarding his paternal grandparents. Both parents are alive. The father, when a boy,

¹ The expenses in connection with this paper were defrayed by a grant from the Carnegie Trust.

suffered from bleeding at the nose, and had great difficulty in getting bleeding from cuts and scratches to stop. He suffered most severely about the age of 15, but since reaching the age of 24 he has had no further symptoms. He is now 53. The mother is a healthy, plethoric-looking woman of 53. She says she has had severe floodings at her confinements, and sometimes bleeds at the nose. Her family is as follows:—

1. A still-born baby.
2. Male, aged 24, healthy.
3. Female, aged 22, chlorotic.
4. Male, aged 20, suffers from severe epistaxis at frequent intervals.
5. Male, aged 2, died of convulsions.
6. Female, aged $8\frac{1}{2}$ months, died of convulsions.
7. Male, aged 14, died of hæmophilia (present case).
8. Male, aged 13, plethoric, has occasional epistaxis.

Previous Illnesses.—Patient cut his forehead with a bottle, and again cut his knee when he was 10, but on neither occasion was there any difficulty in arresting the hæmorrhage.

When he was 12 he began to suffer from epistaxis.

Present Illness.—Epistaxis began on November 1st. It was treated for ten days at home, and then patient was admitted to the Ear and Throat Department of the Infirmary. In spite of local applications, the bleeding continued at intervals, and a fortnight later patient was transferred to Ward 31.

State on Admission.—Patient looked well-nourished, but was markedly anæmic. Temperature, 98° F. Lips and gums very pale. Tongue furred. Teeth good. Bowels regular. No enlargement of the spleen or lymphatic glands. Hæmic murmurs could be heard all over the heart. Pulse, 116 per minute, regular in time and force. Volume small. Tension very low. There were no petechial hæmorrhages. Urine pale, sp. gr. 1025, acid, contained no abnormal constituent. There were no retinal hæmorrhages.

Course.—The bleeding from the nose continued at intervals. Styptic applications and plugging did not seem to be of much avail. Bland's capsules were administered internally. Patient rapidly became weaker, and sickness supervened, making it

impossible to give remedies by the mouth. Temperature rose a little each night, but was never above 100° F. As a last resort, on December 10th, transfusion of salt solution was tried, but death occurred on the morning of December 11th.

Blood Examination.

		Red cells.	Hb.	White cells.
Nov. 22nd,	.	560,000	22	7000
„ 23rd,	.	675,000	24	4063
„ 24th,	.	680,000	24	6250
Dec. 2nd,	.	595,000	18	4000
„ 9th,	.	295,000	12	4400
„ 10th,	.	300,000	—	—

The coagulation time was roughly estimated on several occasions by stroking a drop of blood kept on a slide at room temperature with a needle. Usually half an hour elapsed before a thread of fibrin was drawn out, but on December 9th, fifty minutes elapsed before any fibrin formation occurred.

On December 9th, the blood looked pale and watery. Rouleau formation seemed slightly impaired. The red cells were pale, but showed only a slight degree of poikilocytosis. There was no polychromatophilia. The leucocytes did not give the glycogen reaction.

Differential counts were as follows:—Polymorphs, 64; large lymphocytes, 2; small lymphocytes, 32; transitionals, 2; eosinophils, 0; myelocytes, 0.

Five normoblasts were seen in counting 500 leucocytes.

On December 10th, immediately after transfusion, the differential counts in the above order were 66, 4, 27, 2.5, 0, 0. Two megaloblasts and eight normoblasts were seen in counting 500 leucocytes.

On December 11th, just before death, the films showed much more poikilocytosis. Differential counts gave percentages of 41, 19.5, 39, 0, 0, .5.

Fifteen megaloblasts and forty normoblasts were seen in counting 500 leucocytes.

A *Section* was made on December 12th by Dr Stuart M'Donald.

All the tissues and organs were exceedingly pale. The

heart contained some loose red clot, was extremely fatty, and showed some petechiæ, especially on the anterior surface of the right ventricle. No other hæmorrhages were found.

The liver gave the free iron reaction with potassium ferrocyanide and hydrochloric acid.

The spleen was small and firm.

The intestine showed a dark slatey-grey coloration, and throughout the mesentery were little reddish points, evidently small hæmolympth glands, and there were a few old calcareous tubercular glands.

The bone-marrow of the femur showed red transformation extending from the extremities, but the central part of the shaft contained ordinary yellow marrow.

The brain was anæmic, but showed no other change.

Some Observations on the Blood.

A sample of blood was obtained from the femoral vein about thirty hours after death. There was no coagulation.

(a) A column of blood measuring 5.5 cm. in a test tube of 1 cm. diameter yielded only 1 cm. of corpuscles when centrifuged. This tube was allowed to stand at room temperature, and about four hours after the blood had been removed from the body a loose coagulum formed from the surface of the fluid down to the level of the corpuscles.

(b) Some of the fluid was pipetted off. The addition of a drop of healthy blood to it caused no further coagulation, but merely formed a small clot by itself at the foot of the tube. Healthy corpuscles were very little altered by treatment with the hæmophilic serum.

(c) A specimen of healthy blood was found by Wright's coagulometer to coagulate in five minutes. By means of the leucocyte-counting pipette, 1 part of hæmophilic serum was added to 4 parts of this healthy blood. The mixture of blood and serum was found to coagulate in five minutes, as the healthy blood alone had done.

Histological Examination.

Parts of the organs were preserved in formal-alcohol, to which a few corrosive crystals had been added. Sections were

cut in paraffin and stained with eosine and methylene blue, and (for iron) with ferrocyanide of potassium and hydrochloric acid, with carm-alum as a counter-stain.

Stomach.—Showed no change. Both kinds of glandular cells were well preserved. The sub-mucosa was rich in lymphoid tissue. Iron absent.

Small Intestine.—Villi desquamated. Epithelium at fundus of glands well preserved. Great invasion of mucosa with micro-organisms. There were numerous basophils in the sub-mucosa.

Liver.—Very bloodless, marked fatty degeneration.

Capillaries considerably dilated, but did not contain any abnormal cells. A moderate amount of granular pigment, all of which gave the iron reaction, was seen in the liver cells towards the periphery of the lobules.

Pancreas.—Healthy.

Heart.—Muscle fibres showed marked fatty degeneration.

Lungs.—Slight catarrhal change in the air vesicles.

Kidneys.—Practically healthy. No pigmentary change.

Supra-renal Bodies.—Healthy.

Spleen.—Malpighian bodies well marked, but very few cells showed mitosis. Pulp very bloodless. It contained mainly lymphocytes, but also a few granular cells and a few normoblasts. Scattered throughout the pulp there were large rounded masses of pigment, some as large as an erythrocyte, singly or in aggregations, mostly contained in endothelial cells.

Lymph Glands.—Showed no change. Germ centres not active.

Hæmolymph Glands.—In the blood sinuses were some large cells containing pigment. Only a very small proportion of the pigment gave the iron reaction. The small red bodies in the mesentery proved to be hæmolymph glands.

Thymus.—The lymphoid tissue was encroached on by fat to such an extent as to almost obliterate the lobular arrangement. The lymphoid tissue was fairly uniform, and did not show any packing of cells at the periphery of the lobules.

The Hassall's corpuscles were very numerous and in some cases enormously large. They consisted almost entirely of degenerated epithelial cells, which did not show any concentric

arrangement. In one or two cases the epithelial cells were remarkably distinct and showed no regeneration.

Bone-Marrow.—Both sections and films were examined. The fat was not very greatly encroached on. The most numerous cells were lymphocytes. There were also a few myelocytes, some with eosinophil granules. A few basophils were seen. Red cells were few. Many of those present were normoblasts. A very few atypical megaloblasts were noticed. Giant cells were few and small. A few large cells acting as phagocytes to red corpuscles were seen. There was no pigment.

Sections taken from the extremity of the shaft of the femur only differed from those taken nearer the middle of the bone in the extent to which the fat was encroached on. No difference could be detected in films taken from the two situations.

Vessels.—Sections of the aorta, saphenous vein, and a small artery running beside it were made. The vessels in the fat around lymph glands and in the organs were carefully examined, but no abnormality could be detected.

The capillaries seemed healthy, and the dermis contained the usual amount of elastic tissue.

In this case the tendency seems to have been inherited from the father. The mother, a plethoric-looking woman, cannot be regarded as a true bleeder. The tendency seems also to have been transmitted to two brothers.

The only special features about the symptoms were the persistent epistaxis, and the remarkable absence of any great change in the blood beyond the length of coagulation time and the anæmia until the patient became moribund. The blood after death showed a very great delay in coagulation, but the coagulum that eventually formed seemed to be in about normal amount. It is a matter of regret that I had not the opportunity of trying to artificially hasten the process by the addition of healthy blood, etc. The more important post-mortem appearances were an exhausted bone-marrow showing slight phagocytosis of red cells, the presence of iron pigment in the liver and spleen and the large Hassall's corpuscles in the thymus.

The thymus presented appearances that would probably have been normal in a younger child. No great importance need therefore be attached to the changes found.

The phagocytosis of red cells and the presence of iron pig-

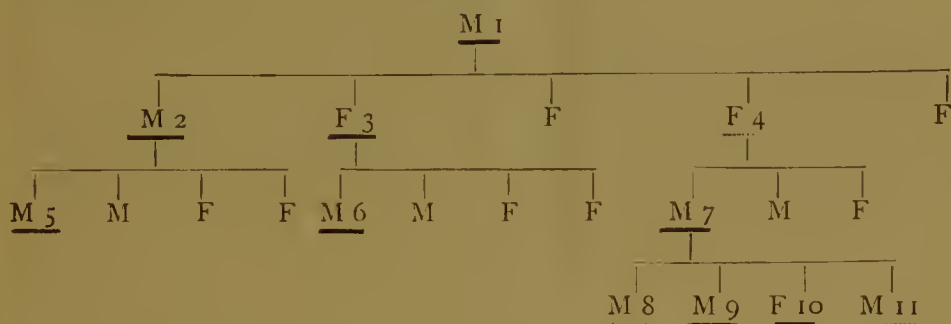
ment in the liver and spleen are probably to be accounted for by the vulnerability of the red corpuscles produced by an exhausted marrow. All the evidence to be derived from this case goes to indicate that the essential pathology of hæmophilia consists in a delayed coagulability of the blood and not in any anatomical peculiarity of vessels or tissues.

I am indebted to Dr James for permission to make use of this case, and to his house-physicians for some of the earlier blood-counts.

II.—A Hæmophilic Genealogy.

The following remarkable genealogy has recently come to my knowledge.

The males are denoted by the letter "M"; the females by "F." The letters are underlined in the case of the bleeders. The dotted lines indicate a slight tendency to hæmophilia. The numbers are for reference.



In all probability the tendency existed further back than the four generations indicated, but the evidence available is merely legendary. All the cases are direct descendants of the original great-grandfather, M 1, and in no case was there intermarriage with another hæmophilic stock.

In spite of suffering severely all his life from epistaxis and other forms of hæmorrhage, M 1 lived till well over 80.

M 6 died of hæmorrhage. M 7 suffered severely from hæmorrhages when a boy, but outgrew the tendency.

His three sons in early life showed the tendency in a minor degree, while the daughter (F 10) has on several occasions suffered to a dangerous extent from hæmorrhages.

I have recently examined the blood in the case of M 11, aged 22. Nothing abnormal was found. Coagulation time,

tested at blood heat with Wright's apparatus, was found to be just over four minutes. Red blood corpuscles numbered 5,360,000 and white cells 6800 per c.mm. Polymorphs were 71, lymphocytes 27, and eosinophils 2 per cent.

III.—Some Recently Published Genealogies.

Hæmophilia is stated to be a hereditary disease usually affecting males, but transmitted through the female line. This is well illustrated in the work of Grandidier (1) and Legg (2). The foregoing cases, however, are examples of transmission through the male line, and in the fourth generation of the second family we find a striking reversal of the usual incidence, viz., transmission through the male and the disease showing most markedly in the female.

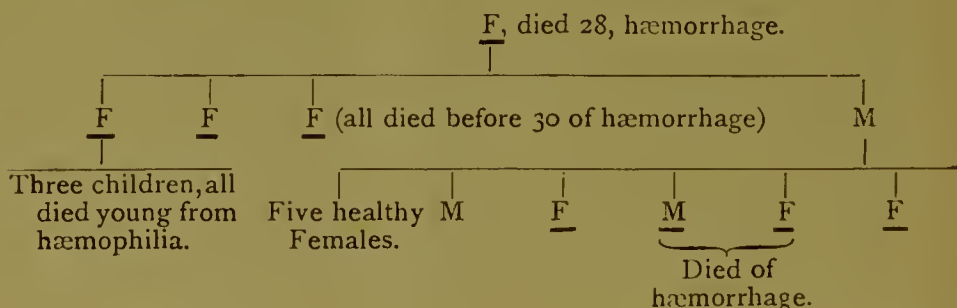
I find that a departure from the classical description as regards sex and heredity is a feature of some of the cases recorded during the last eighteen months.

Ferrier (3) mentions two cases in females, but gives no details regarding their history.

Blaker (4) describes a case in a female child of eleven months where the tendency was transmitted from patient's paternal grandmother, a bleeder, to two aunts, but the child's father did not show symptoms.



Pearson (5) records a remarkable instance of the condition affecting the female members of a family, and showing transmission through the male line.



Histology and Genealogy of Hæmophilia 141

On the other hand, cases in accord with the usual heredity are recorded by Abderhalden (6) and Faludi (7), though the mother in the case of the latter suffered from epistaxis. Grant (8) also records a case which presumably comes under this category, as he states that the boy came of a family of bleeders, and was treated with ovarian extract, on the ground of the rarity of the condition in females.

A case is recorded by Monsarratt (9) in which there was no family history of the condition at all. This case was a boy, aged 8, who fractured his femur, but a good result followed in spite of enormous effusion at the seat of the injury.

IV.—Some Recent Views on Pathology.

The views that have been expressed regarding the pathology of hæmophilia are very diverse.

Ferrier (3) considers the condition to be due to a decalcification of the blood along with the teeth, etc., associated with phosphaturia, due to such conditions as hyperchlorhydria and excess of acid diet, and obtained good results by giving calcium.

Wallis (10) has also described cases of hæmophilia in whom extraction of teeth became a safe operation after the use of calcium chloride.

Wright (11) found that he could reduce the coagulation time not only in a hæmophilic, but also in healthy persons, by the use of this substance, and Schäfer (12) has recommended its addition to suprarenal substance in styptic lotions.

On the other hand, good results have not always followed its exhibition, and Legg (13) states that he has never seen anything like complete disappearance of symptoms even after a prolonged course of it.

Abderhalden (6) found that wounds of the skin did not bleed excessively in his case, while wounds of mucous membrane did so, and concludes that hæmophilia is due to disease of the small vessels and capillaries.

Geyer (14) found an enormous number of nucleated red cells in one case, and considers that clotting is prevented by the degeneration products of such cells, but thinks that thinness of vessel walls, their inability to retract, their want of muscle

fibres and the scarcity of elastic fibres in the skin are all factors of importance!

Faludi (7), in the case of a boy of 6, could find no anatomical ground to explain the condition.

V.—Conclusions.

From these notes the following conclusions may be drawn:—

1. Hereditary transmission is a striking feature in nearly every case.
2. Although hæmophilia is more common in males, it is not so infrequent in females as is generally stated.
3. A large proportion of the more recently recorded cases have been transmitted through the male line.
4. The condition is not due to any anatomical peculiarity of vessels or tissues demonstrable by present methods.
5. The essential pathology seems to consist in a greatly delayed coagulability of the blood which progresses with progressing anæmia.
6. There is reason to believe that calcium chloride may be of service, but its use is likely to be limited in severe cases by the irritability of the stomach and its nauseous taste.

REFERENCES.

1. Grandidier. *Schmidt's Jahrbücher der in- und ausländischer Gesammten Medicin*, 173, 1877, p. 185.
2. Legg. *St Bart's Hosp. Reports*, 67, 1881, p. 303.
3. Ferrier. *Comptes Rendus Hebdomadaires des Séances de la Société de Biologie*, 55, 1903, p. 937.
4. Blaker. *Brit. Med. Journ.*, January 23, 1904, p. 189.
5. Pearson. *Lancet*, January 9, 1904.
6. Abderhalden. *Ziegler's Beiträge*, Bd. 35, S. 213.
7. Faludi. *Arch. f. Kinderheilkunde*, 39, 1904, p. 92.
8. Grant. *Lancet*, November 5, 1904.
9. Monsarratt. *Brit. Journ. for Children's Diseases*, November 1904.
10. Wallis. *Brit. Med. Journ.*, May 10, 1902, p. 1141.
11. Wright. *Brit. Med. Journ.*, 1893, ii. p. 223.
12. Schäfer. *Brit. Med. Journ.*, April 27, 1901.
13. Legg. "Allbutt's System," v. p. 548.
14. Geyer. *Medizinskoje Obosrenige*, 1904, 1; quoted *Folia Hæmologica*, i., 1904, p. 579.

